Diabetes Mellitus

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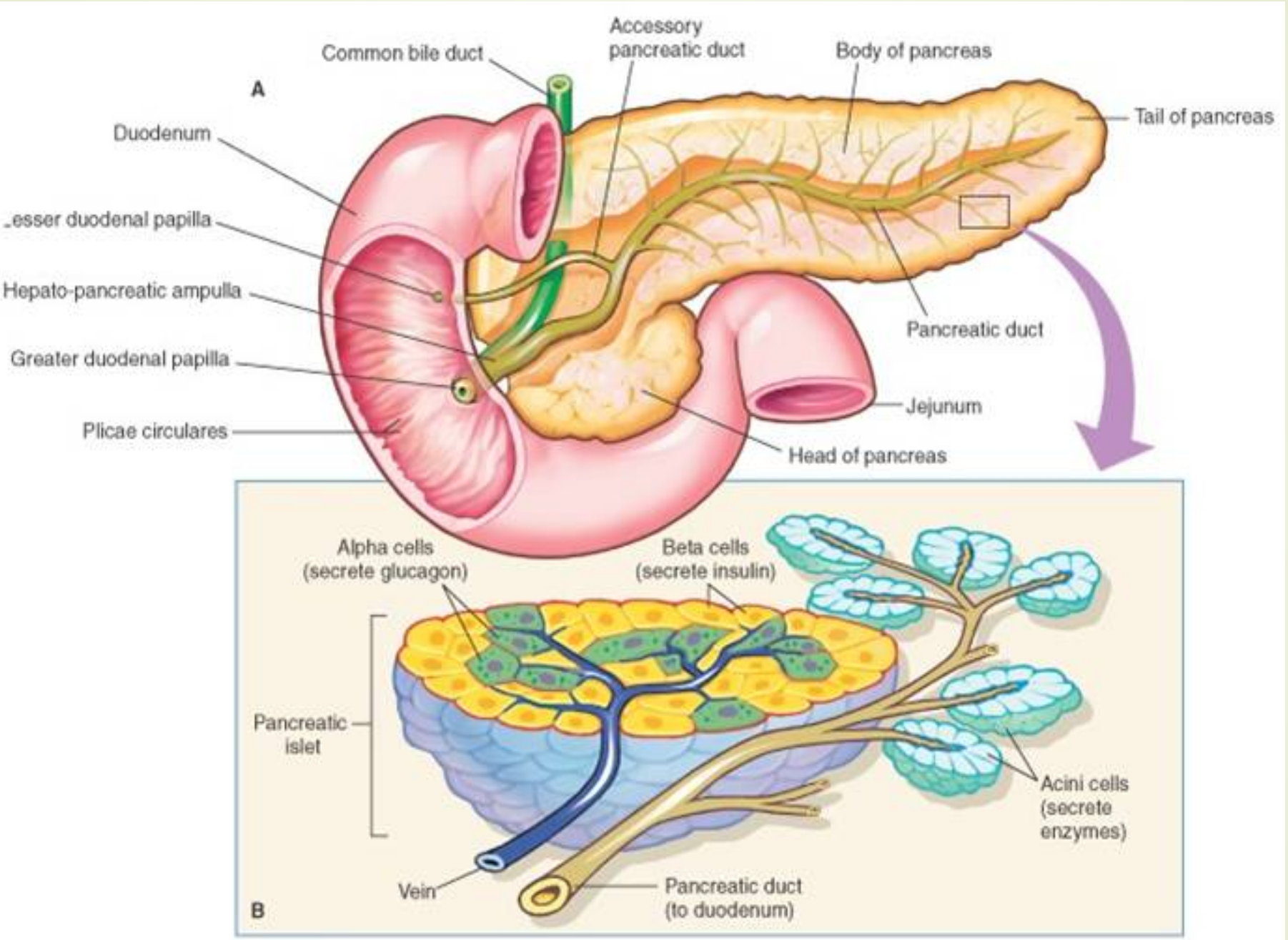
Objectives

- Understand the structure of the pancreas and have a basic understanding of its function.
- The student should have an understanding of the pathogenesis and major histopathological changes seen in diabetes mellitus type 1 and type 2.
- The student should recognize the major complications of diabetes mellitus.


A
Common bile duct
Accessory pancreatic duct
Body of pancreas
Tail of pancreas
Duodenum
Lesser duodenal papilla
Hepato-pancreatic ampulla
Greater duodenal papilla
Plicae circulares
Pancreatic duct
Jejunum
Head of pancreas
B
Alpha cells (secrete glucagon)
Beta cells (secrete insulin)
Pancreatic islet
Acini cells (secrete enzymes)
Vein
Pancreatic duct (to duodenum)

THE ENDOCRINE PANCREAS

- ***islets of Langerhans*, contain four major cell types :β, α, δ, and PP (pancreatic polypeptide) cells.**
- *The β cell produces insulin*
- *The α cell secretes glucagon .*
- δ cells contain somatostatin
- *PP cells contain a unique pancreatic polypeptide.* VIP, that exerts several gastrointestinal effects, such as stimulation of secretion of gastric and intestinal enzymes

Diabetes Mellitus (DM)

*Diabetes mellitus is not a single disease entity but rather a *group of metabolic disorders sharing the common underlying feature of* ***hyperglycemia*****.**

***Hyperglycemia in diabetes results from defects in insulin secretion, insulin action, or, most commonly, both.**

***Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations**

Diabetes Mellitus (DM)

Prediabetes, **defined as elevated blood sugar that does not reach the criterion accepted for an outright diagnosis of diabetes ;**

persons with prediabetes have an elevated risk for development of frank diabetes

Diagnosis of DM

- Blood glucose levels normally are maintained in a very narrow range, usually 70 to 120 mg/dL.
- The diagnosis of diabetes is established by elevation of blood glucose by any one of three criteria:

1) A random blood glucose concentration of 200 mg/dL or higher, with classical signs and symptoms

2) A fasting glucose concentration of 126 mg/dL or higher on more than one occasion

3)An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is 200 mg/dL or higher 2 hours after a standard carbohydrate load (75 g of glucose).

- those with serum fasting glucose greater than 110 but less than 126 mg/dL, or OGTT values of greater than 140 but less than 200 mg/dL, are considered to have *impaired glucose tolerance*, also known as *prediabetes*.

- Persons with impaired glucose tolerance have a significant risk for progression to overt diabetes over time

Classification of DM

1. Type 1 Diabetes
Beta cell destruction, usually leading to absolute insulin deficiency
2. Type 2 Diabetes
Combination of insulin resistance and beta cell dysfunction
3. Genetic Defects of Beta Cell Function
Maturity-onset diabetes of the young (MODY), caused by mutations in: Hepatocyte nuclear factor 4α gene (*HNF4A*)—MODY1 Glucokinase gene (*GCK*)—MODY2 Hepatocyte nuclear factor 1α gene (*HNF1A*)—MODY3 Pancreatic and duodenal homeobox 1 gene (*PDX1*)—MODY4 Hepatocyte nuclear factor 1β gene (*HNF1B*)—MODY5 Neurogenic differentiation factor 1 gene (*NEUROD1*)—MODY6
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (3243A→G)
Defects in proinsulin conversion
Insulin gene mutations
4. Genetic Defects in Insulin Action
Insulin receptor mutations
5. Exocrine Pancreatic Defects
Chronic pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy

6. Endocrinopathies
Growth hormone excess (acromegaly)
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
7. Infections
Cytomegalovirus infection
Coxsackievirus B infection
Congenital rubella
8. Drugs
Glucocorticoids
Thyroid hormone
β-Adrenergic agonists
9. Genetic Syndromes Associated with Diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
10. Gestational Diabetes Mellitus
Diabetes associated with pregnancy

Type 1 DM

- ***Type 1 diabetes (T1D)*** **is characterized by an absolute deficiency of insulin secretion caused by pancreatic beta cell destruction, usually resulting from an autoimmune attack.**
- **Type 1 diabetes accounts for approximately 10% of all cases.**

Type 2 DM

- ***Type 2 diabetes (T2D)*** **is caused by a combination of peripheral resistance to insulin action and an inadequate compensatory response of insulin secretion by the pancreatic beta cells (*relative insulin deficiency*).**
- **Approximately 80% to 90% of patients have type 2 diabetes.**

Pathogenesis

- **Type 1 diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens.**
- The classic manifestations of the disease occur late in its course, after more than 90% of the beta cells have been destroyed. **The fundamental immune abnormality in type 1 diabetes is a failure of self-tolerance in T cells.**
- **autoantibodies** against a variety of beta cell antigens, are detected in the blood of 70% to 80% of patients.
- 90% and 95% of white patients with type 1 diabetes have ***HLA-DR3, or DR4***
- **environmental factors,** especially infections, may be involved in type 1 diabetes.

PATHOGENESIS

Type 2 diabetes is a prototypical complex multifactorial disease.

*Environmental factors, such as a sedentary life style and dietary habits.

*Genetic factors are also involved in the pathogenesis,

recent large-scale genome-wide association studies, have identified more than a dozen susceptibility loci called "diabetogenic" genes.

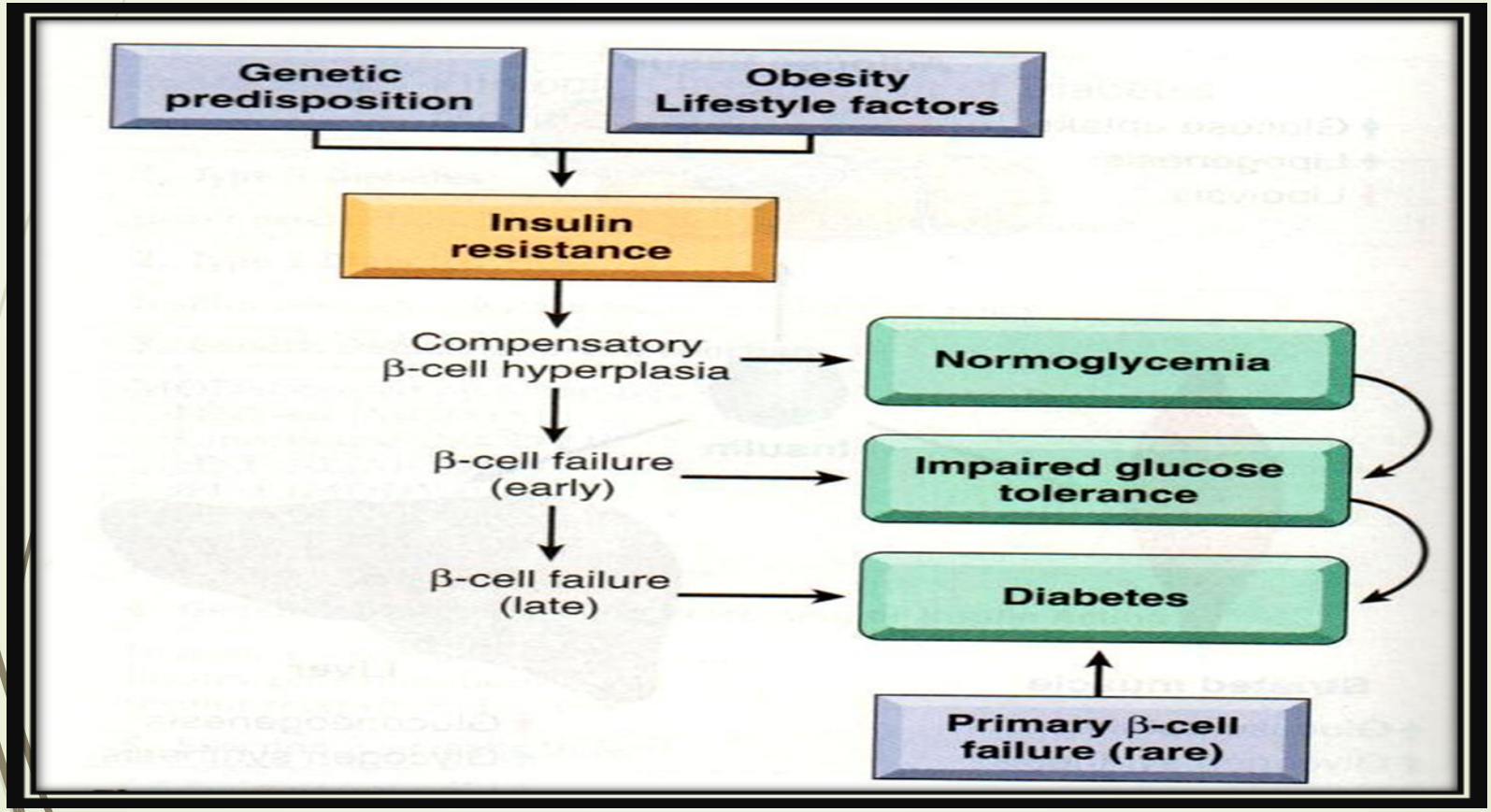
- The two metabolic defects that characterize type 2 diabetes are

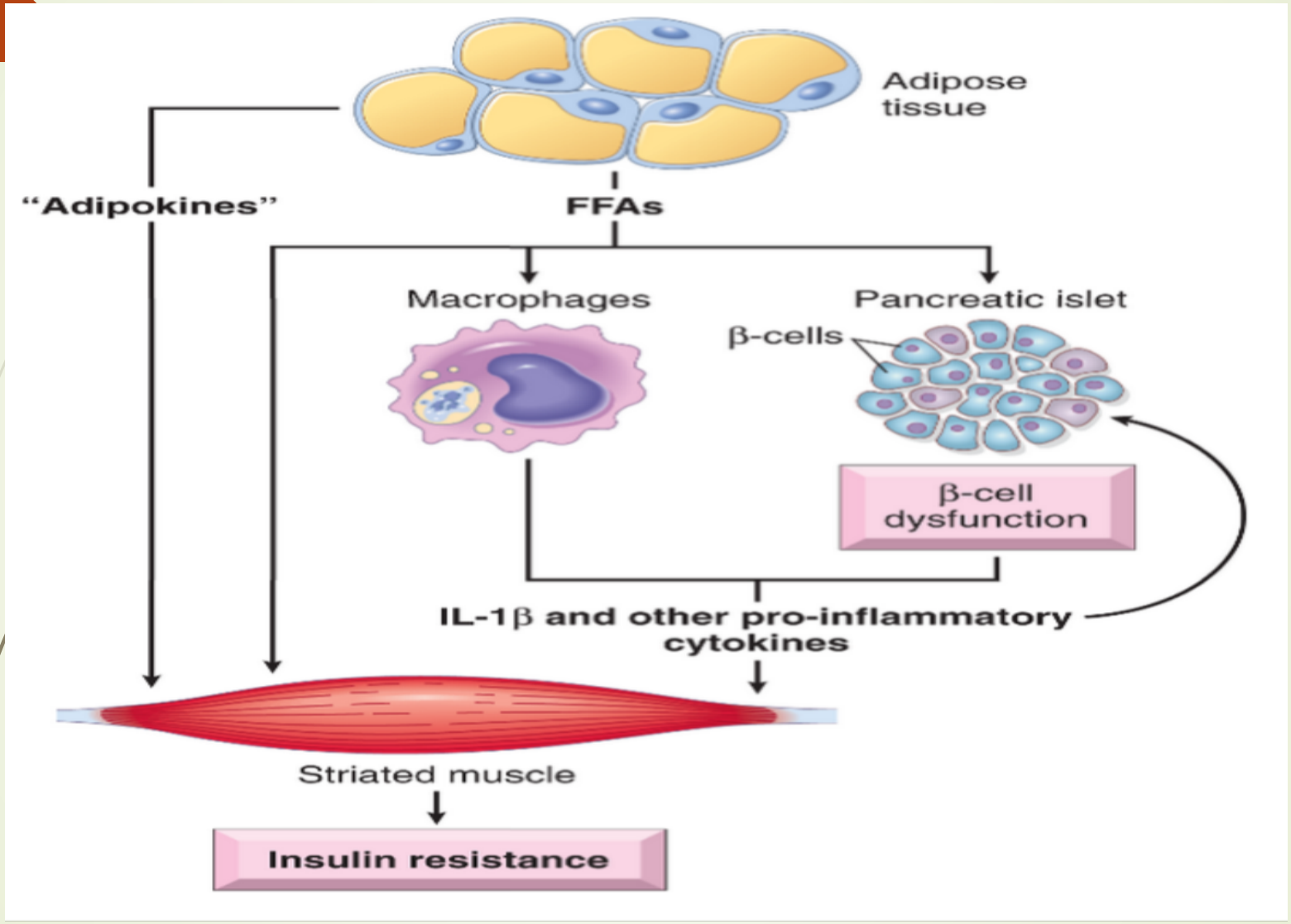
(1) a decreased ability of peripheral tissues to respond to insulin (insulin resistance)

(2) beta cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycemia

- ***Insulin resistance*** **is defined as the failure of target tissues to respond normally to insulin. It leads to decreased uptake of glucose in muscle.**

Obesity and Insulin Resistance




Adipose tissue
"Adipokines"
FFAs
Macrophages
Pancreatic islet
β-cells
β-cell dysfunction
IL-1β and other pro-inflammatory cytokines
Striated muscle
Insulin resistance

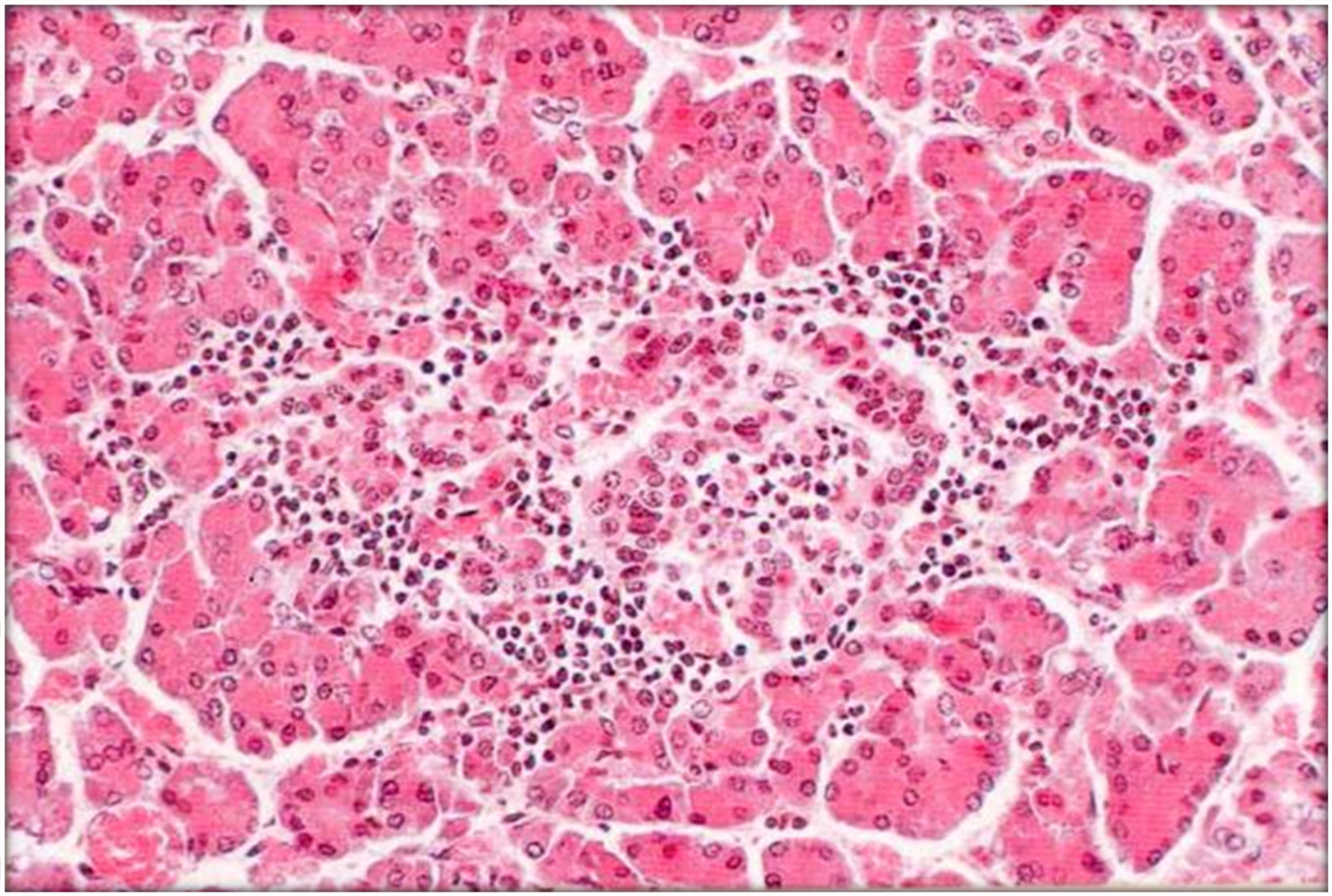
Monogenic Forms of Diabetes

- Type 1 and type 2 diabetes are genetically complex ,no single-gene defect (mutation) can account for predisposition to these entities.
- By contrast, monogenic forms of diabetes are uncommon examples of the *diabetic phenotype occurring as a result of loss-of-function mutations within a single gene*.
- The largest subgroup of patients in this category traditionally was designated as having ***maturity-onset diabetes of the young*** *(MODY)* because of its superficial resemblance to type 2 diabetes and its occurrence in younger patients
- MODY can be the result of inactivating mutations in one of six genes

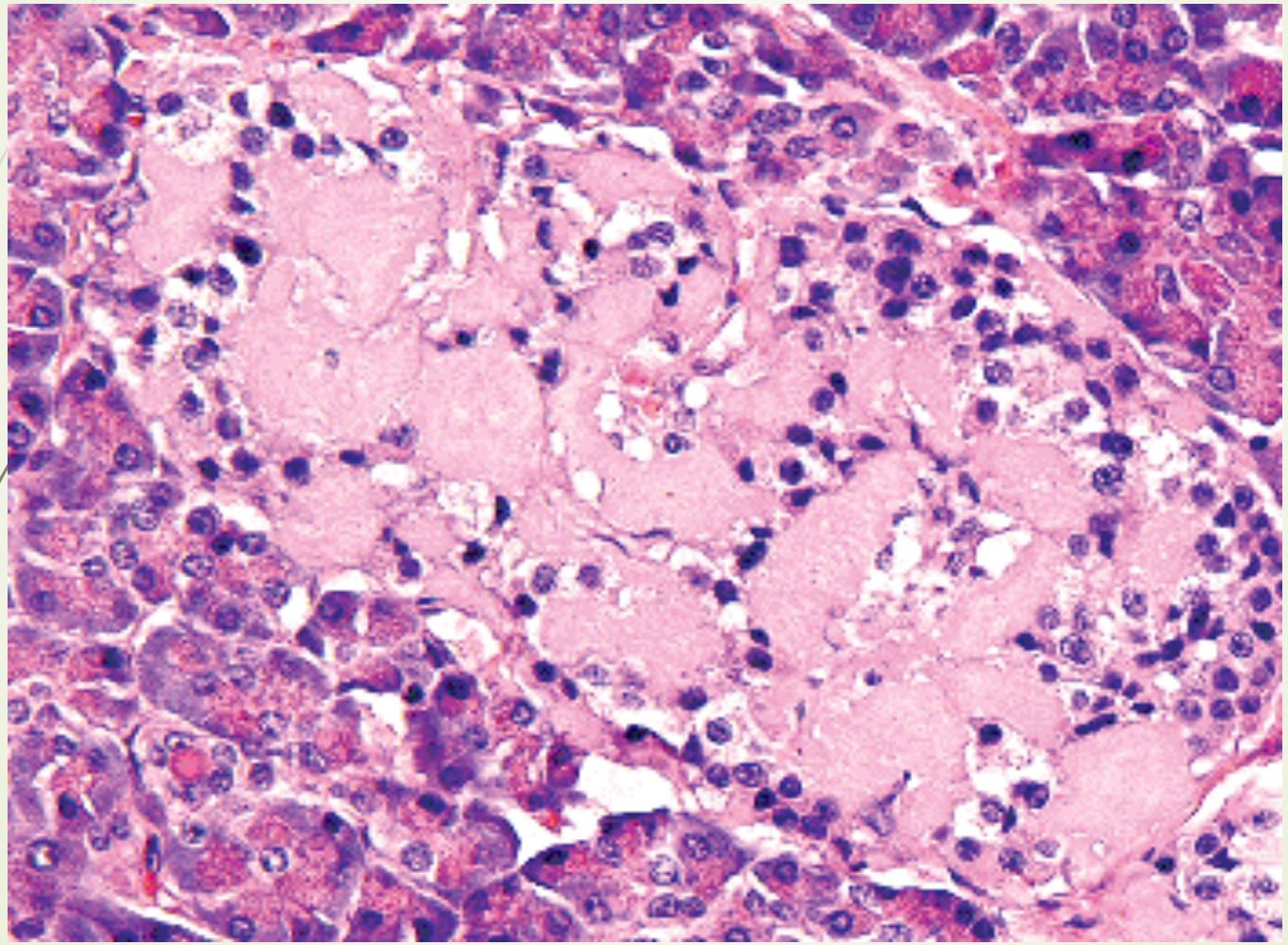
Morphology

- Lesions in the pancreas are inconstant and rarely of diagnostic value. One or more of the following alterations may be present:
- **Reduction in the number and size of islets.** This change most often is seen in type 1 diabetes.
- **Leukocytic infiltration of the islets,** which are principally composed of mononuclear cells (lymphocytes and macrophages). it is typically more in Type1 DM.
- **Amyloid replacement of islets in long-standing type 2 diabetes,** appearing as deposition of pink, amorphous material. At advanced stages fibrosis also may be observed

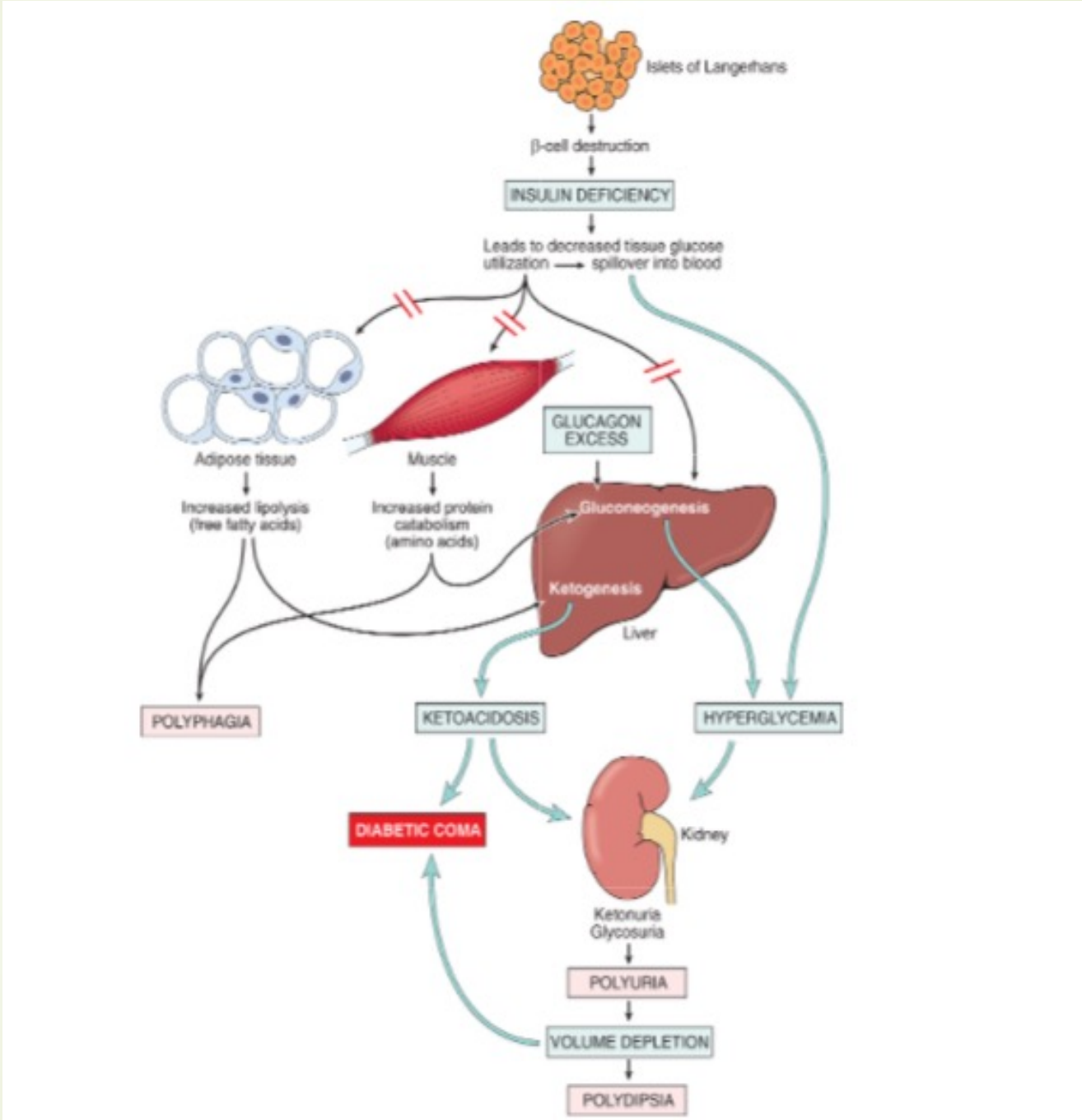
Insulitis



Amyloidosis



Clinical manifestations



Hyperglycemia
Glycosuria
Loss of calories
Ployuria
Hunger
Weight loss
Mobilization of fat and protein
Loss of electrolytes
Dehydration
Polyphagia
Acidosis
Polydipsia
Negative nitrogen balance
Hyperpnea
Coma and Death

Type 1 DM

the classic triad of diabetes: *polyuria, polydipsia,* and *polyphagia*. Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness.

- In patients with type 1 diabetes, deviations from normal dietary intake, unusual physical activity, infection, or any other forms of stress may rapidly influence the metabolic balance, predisposing the affected person to *diabetic ketoacidosis*.
- The plasma glucose usually is in the range of 500 to 700 mg/dL
- The marked hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state.

Type 2 DM

- *Type 2 diabetes mellitus* also may manifest with polyuria and polydipsia, but unlike in type 1 diabetes, patients often are older than 40 years and frequently are obese.
- In the decompensated state, patients with type 2 diabetes may develop *hyperosmolar nonketotic coma*. This syndrome is engendered by severe dehydration resulting from sustained osmotic diuresis and urinary fluid loss due to chronic hyperglycemia. Typically, the affected person is an elderly diabetic who is disabled by a stroke or an infection and is unable to maintain adequate water intake.

Table 19–6 Type 1 Versus Type 2 Diabetes Mellitus

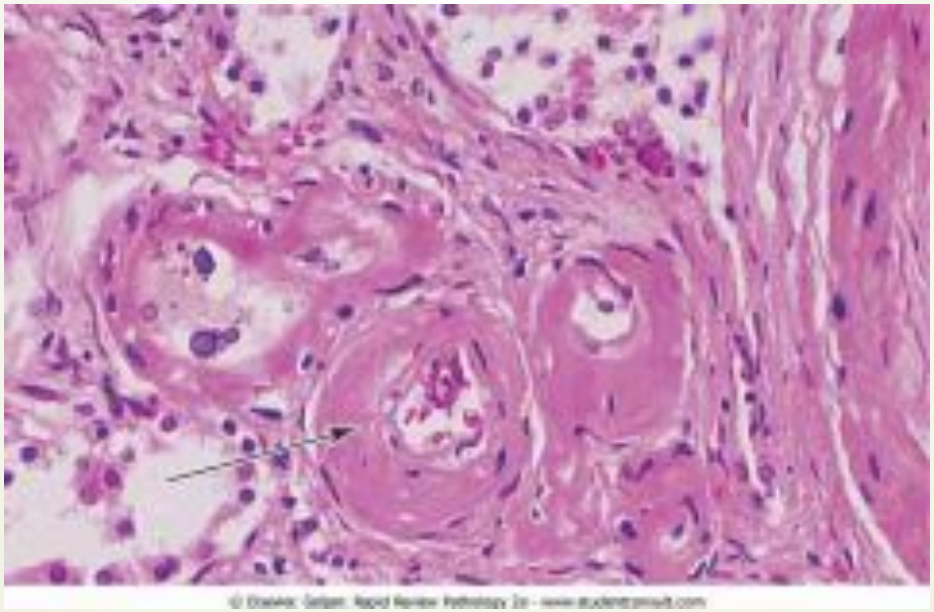
Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset usually in childhood and adolescence	Onset usually in adulthood; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority of patients are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma
Genetics	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes
Pathogenesis	
Dysfunction in regulatory T cells (Tregs) leading to breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by beta cells Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Autoimmune "insulitis"	*Early*: inflammation; *late*: amyloid deposition in islets
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, human leukocyte antigen; MHC, major histocompatibility complex.

Diabetic complications: Macrovascular Disease.

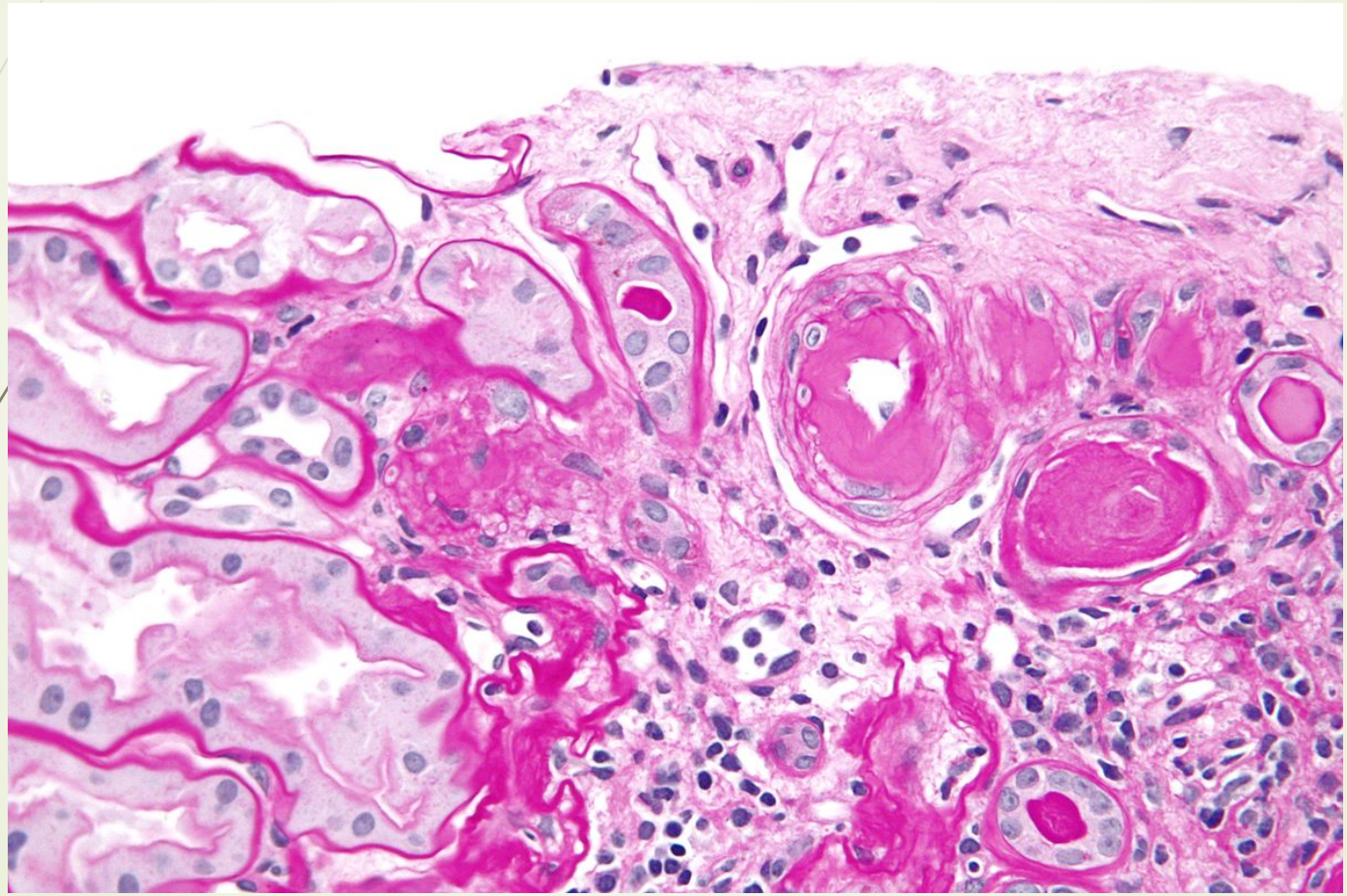
- The hallmark of diabetic macrovascular disease is accelerated atherosclerosis affecting the aorta and large and medium-sized arteries.
- Myocardial infarction, caused by atherosclerosis of the coronary arteries, is the most common cause of death in diabetics
- Gangrene of the lower extremities, as a result of advanced vascular disease
- The larger renal arteries also are subject to severe atherosclerosis, but the most damaging effect of diabetes on the kidneys is exerted at the level of the glomeruli and the microcirculation.

- **Hyaline arteriolosclerosis,** the vascular lesion associated with hypertension , is both more prevalent and more severe in diabetics than in nondiabetics
- It takes the form of an amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen



Diabetic complication: Microangiopathy.

- One of the most consistent morphologic features of diabetes is **diffuse thickening of basement membranes.** The thickening is most evident in the capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla
- the basal lamina separating parenchymal or endothelial cells from the surrounding tissue is markedly thickened by concentric layers of hyaline material composed predominantly of type IV collagen . Of note, **despite the increase in the thickness of basement membranes, diabetic capillaries are more leaky than normal to plasma proteins.**
- **The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.**



Diabetic complication: Nephropathy

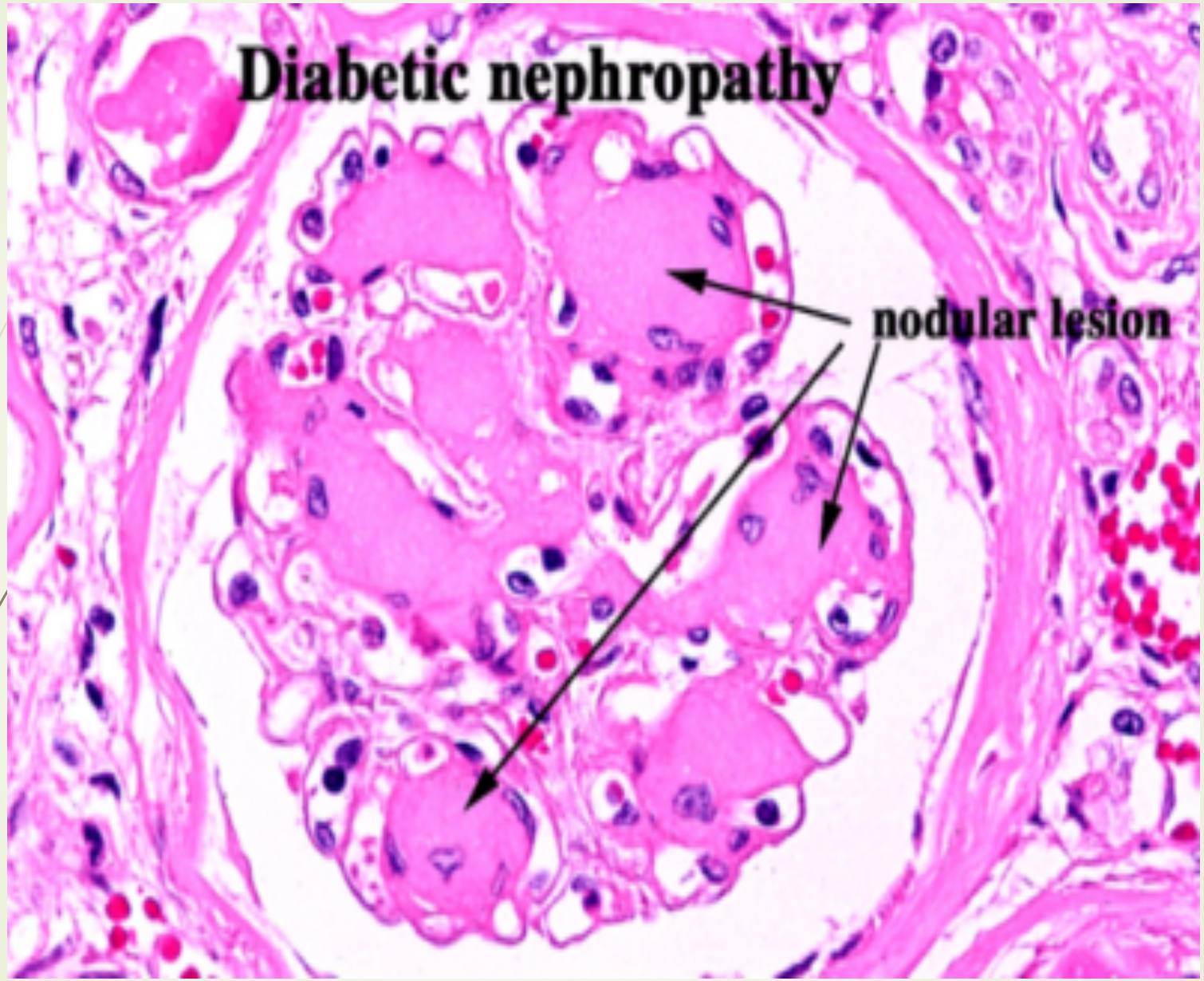
- Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered:
- (1) glomerular lesions;
- (2) renal vascular lesions, principally arteriolosclerosis
- (3) pyelonephritis, including necrotizing papillitis.

Diabetic complication: Nephropathy

- The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis.
- The glomerular capillary basement membranes are thickened along their entire length.
- **Diffuse mesangial sclerosis** consists of a diffuse increase in mesangial matrix along with mesangial cell . When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema

Diabetic complication: Nephropathy

- **Nodular glomerulosclerosis** : ball-like deposits of a laminated matrix situated in the periphery of the glomerulus . These nodules are PAS-positive . This distinctive change has been called the **Kimmelstiel-Wilson lesion.**
- Nodular glomerulosclerosis is encountered in approximately 15% to 30% of persons with long-term diabetes. It is essentially pathognomonic of diabetes.
- Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular-appearing cortical surface


Diabetic nephropathy
nodular lesion

Ocular Complications of Diabetes.

- **The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma.**
- Retinopathy, the most common pattern
- **The lesion in the retina takes two forms: **nonproliferative (background) retinopathy**

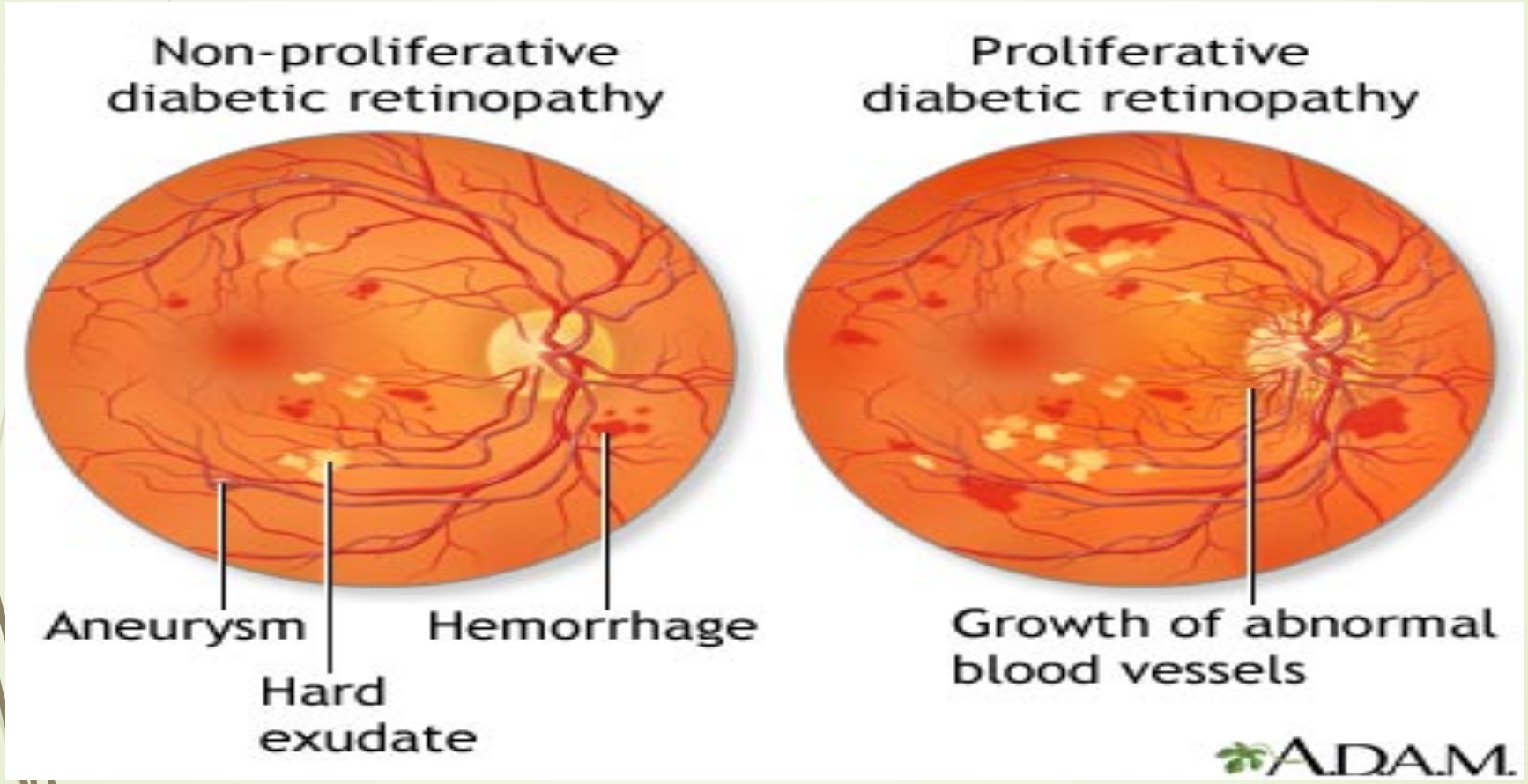
  **** proliferative retinopathy.**

Nonproliferative retinopathy:

- hemorrhages, retinal exudates (cotton wool sots), microaneurysms, edema, thickening of the retinal capillaries (microangiopathy).
- The microaneurysms are discrete saccular dilations of retinal choroidal capillaries that appear through the ophthalmoscope as small red dots.

Proliferative retinopathy is a process of neovascularization and fibrosis.

- This lesion leads to serious consequences, including blindness, especially if it involves the macula and retinal detachment


Non-proliferative diabetic retinopathy
Proliferative diabetic retinopathy
Aneurysm
Hard exudate
Hemorrhage
Growth of abnormal blood vessels
A.D.A.M.

Diabetic Neuropathy.

- The central and peripheral nervous systems are not spared by diabetes.
- The most frequent pattern of involvement is that of a peripheral, symmetric neuropathy of the lower extremities affecting both motor and sensory function, particularly the latter.
- Other forms include autonomic neuropathy, which produces disturbances in bowel and bladder function and diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop .
- **Microvasculopathy involving the small blood vessels of nerves contributes to the disorder.**

- Diabetic patients have an enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis.
- Such infections cause about 5% of diabetes-related deaths.
- In a person with diabetic neuropathy, a trivial infection in a toe may be the first event in a long succession of complications (gangrene, bacteremia, pneumonia) that may ultimately lead to death

Infections

- Bacterial and Fungal Infections Occur in Diabetic Hyperglycemia if Poorly Controlled
- Renal papillary necrosis may be a devastating complication of bladder infection.
- Mucormycosis: A dangerous infectious complication of poorly controlled diabetes is often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.

Gestational diabetes

- Diabetes Occurring During Pregnancy
- May Put both Mother and Fetus at risk
- Develops in only a few percent of seemingly healthy women during pregnancy.
- It may continue after parturition in a small proportion of these patients.
- These women highly susceptible to overt T2DM later in life.